VINYL AZIDE STRATEGY FOR THE SYNTHESIS OF TETRASUBSTITUTED PYRIMIDINES

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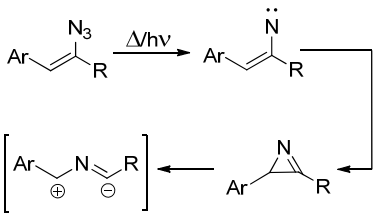
Introduction:

Pyrimidine derivatives are one of the most important biologically active heterocycles. They are known to display antibacterial, antiviral, anticancer, anti-HIV, antimalarial activities, and others. In addition, pyrimidines have found applications in photophysics and polymer chemistry. So, new methods for their synthesis are actively being developed. However they often use specific substrates and/or reagents or harsh conditions.

In the last decade, vinyl azides, in particular α-azidocinnamates (have been widely utilized as a key three-atom synthon for the formation of nitrogen heterocycles such as pyrroles, pyrazines, indoles, etc. Under thermolysis or photolysis, vinyl azides can produce highly strained three-membered heterocycles – 2*H*-azirines which can act as a dipolarophiles or source of highly reactive dipole – nitrile ylides.

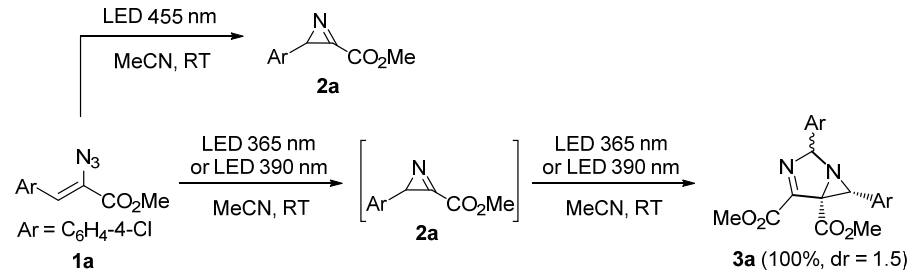


Scheme 1. Transformations of vinyl azides and 2*H*-azirines.

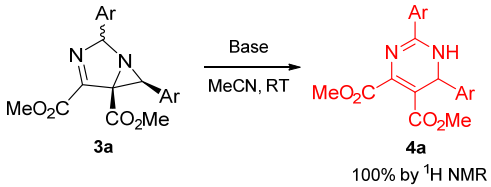
Results and discussion

We investigated the photolysis of representative azidocinnamate **1a** by different LEDs. The irradiation of the representative azidocinnamate **1a** by blue light (455 nm) in MeCN during 2.5 h at RT afforded only azirine **2a.** No any other reaction was observed even after irradiation of the reaction mixture for a long time.

When decreasing wavelength of LED (to 390 and 365 nm) irradiation for 2.5 h led to total conversion of **1a** to two diastereomeric "dimers" of azirine **–** 1,3-diazabicyclo[3.1.0]hex-3-enes **3a.**



Scheme 2. Irradiation of α-azidocinnamate **1a** with 365–455 nm LED.

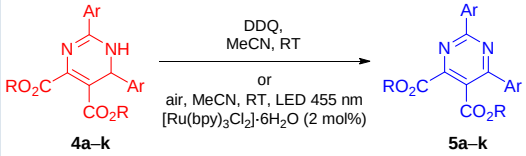


Scheme 3. Isomerization of **3a** into 1,6-dihydropyrimidine **4a**.

Isomerization of two diastereomers of **3a** into 1,6-dihydropyrimidine **4a** in MeCN proceeded in the presence of bases in almost quantitative yield.

Base	Time, min
Pyridine	—
Et_3N	150
1,4-diazabicyclo[2.2.2]octane (DABCO)	100
N-methylmorpholine	15
1,8-Diazabicyclo[5.4.0]undec-7-ene(DBU)	15

Table 1. Isomerization of **3a** into dihydropyrimidine **4a** by different bases.



Scheme 4. Aromatization of 1,6-dihydropyrimidines **4a–k** to pyrimidines **5a–k**

The aromatization of 1,6-dihydropyrimidines **4a–k** can proceed completely in less than one minute using 1 eq. of organic oxidant, 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ), leading to pyrimidines **5a–k.** Oxidation can also occur using photoredox catalysis with 2 mol% of $[Ru(bpy)_3Cl_2]\cdot 6H_2O$ in 4 h (85% yield)

Table 2. Isolated yields of 1,6-dihydropyrimidines **4a–k** and pyrimidines **5a–k**. [a]One-pot procedure from α-azidocinnamate **1**. [b]From dihydropyrimidines **4** using DDQ.

Entry	Ar	R	Yield of 4,[a] %	Yield of 5,[b] %
1	4-ClC_6H_4	Me	97 (**4a**)	95 (**5a**)
2	4-BrC_6H_4	Me	93 (**4b**)	95 (**5b**)
3	4-IC_6H_4	Me	70 (**4c**)	81 (**5c**)
4	2-$MeOC_6H_4$	Me	91 (**4d**)	90 (**5d**)
5	4-$MeOC_6H_4$	Me	91 (**4e**)	85 (**5e**)
6	2,4-$Cl_2C_6H_3$	Me	91 (**4f**)	85 (**5f**)
7	4-MeC_6H_4	Me	93 (**4g**)	90 (**5g**)
8	4-FC_6H_4	Me	94 (**4h**)	90 (**5h**)
9	4-$CF_3C_6H_4$	Me	95 (**4i**)	95 (**5i**)
10	Naphthalen-2-yl	Me	73 (**4j**)	97 (**5j**)
11	4-$MeOC_6H_4$	Bu	42 (**4k**)	97 (**5k**)

Conclusion:

The irradiation of α-azidocinnamates by blue light (455 nm) leads to the formation of 2*H*-azirines only, while the irradiation by violet or UV-A light (365 nm) results in the transformation of the *in situ* formed 2*H*-azirines to 1,3-diazabicyclo[3.1.0]hexenes. Based on these results a one-pot procedure for the synthesis of tetrasubstituted dihydropyrimidine and pyrimidine derivatives from α-azidocinnamates was developed.

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